Title: A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec in Amgen or BioVEX-Sponsored Clinical Trials

Amgen Protocol Number **(Talimogene Laherparepvec) 20120139**

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Date: 01 May 2008
Amendment 1 Date: 11 February 2010
Amendment 2 Date: 25 February 2014
Amendment 3 Date: **18 November 2015**

Investigator's Agreement

I have read the attached protocol entitled **A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec in Amgen or BioVEX-Sponsored Clinical Trials**, dated **18 November 2015,** and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec **in Amgen or BioVEX-Sponsored Clinical Trials**

Study Phase: Not applicable

Indication: Any tumor type eligible for treatment with talimogene laherparepvec in Amgen or BioVEX-sponsored clinical trial

Primary Objective(s): The primary objectives are:

- To evaluate the long-term safety of talimogene laherparepvec
- To monitor subject overall survival
- **To monitor use of subsequent anti-cancer therapy, for the tumor indication in the prior Amgen or BioVEX-sponsored clinical trial, including retreatment with marketed talimogene laherparepvec in subjects previously enrolled in Amgen or BioVEX-sponsored clinical trials**

Hypothesis: A formal hypothesis will not be tested in this study. The goal of this observational registry study is to evaluate the overall survival, **use of subsequent anti-cancer therapy,** and the long-term safety of subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type.**

Study Endpoint(s):

- Long-term safety as assessed by subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest, that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **will be summarized. Talimogene laherparepvec treatment-related adverse events during the retreatment period with marketed talimogene laherparepvec and up to 30 days after the discontinuation of treatment will be reported separately.**
- **Survival status**
- **Use of subsequent anti-cancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial including retreatment with marketed talimogene laherparepvec for approved indication.**

Study Design: This is an international, multicenter, strictly observational registry program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and have ended treatment **and participation, including long-term follow-up, in** that trial. No experimental intervention is involved. Thus, a subject will undergo clinical assessments and receive the standard of care treatment as determined by the subject's physician. Subjects who consent to and are eligible to enroll in this registry study will be monitored 1) for adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec, 2) for overall survival every 3 months (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first, **and 3) use of anti-cancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial including retreatment with marketed talimogene laherparepvec for approved indication**.

If retreatment with **marketed** talimogene laherparepvec **for approved indication** is indicated during participation in the registry study, a subject **will continue to** participat**e** in the registry study **and the retreatment will be reported**.

Sample Size: The total number of subjects who will participate in the registry study will be determined by the number of subjects who remain alive at the end of the previous Amgen or

BioVEX-sponsored talimogene laherparepvec clinical trial in which they participated **for any tumor type** and who consent to and are deemed eligible to participate in this registry study.

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria:

Subject must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and must have discontinued treatment **and follow-up in** that trial. **Subjects that have been retreated with marketed talimogene laherparepvec for approved indication are also eligible to participate in the study**.

Key Exclusion Criteria:

Subject must not be currently receiving talimogene laherparepvec **on an Amgen or BioVEX-sponsored clinical trial**. **Subject currently participating, including for long-term follow-up, in other Amgen-sponsored talimogene laherparepvec clinical trial.**

For a full list of eligibility criteria, please refer to Section 4.

Assessments:

Screening/Enrollment:

The following assessments will be performed during the screening/enrollment period:

- confirmation that the informed consent**/assent** form has been signed
- review of inclusion and exclusion criteria
- recording of protocol history (ie, protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial)
- recording of subsequent anti-cancer therapy **for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial and** that begins after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **and prior to enrollment in the registry study**
- **recording of retreatment with marketed talimogene laherparepvec after end of previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial and prior to enrollment in the registry study**
- recording of adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial

Follow-up Observation Period/End of Study:

The following assessments will be performed via phone or clinic visit every 3 months (± **30** days) during the follow-up observation period until withdrawal of consent, death, or end of study, whichever occurs first:

- **recording of adverse events deemed by the investigator to be related to the treatment with talimogene laherparepvec during the registry study**
- **recording of survival status including date of contact, status (ie, alive or deceased and date/cause of death, if applicable) during the registry study**
- recording of subsequent anti-cancer therapy **for tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial during the registry study**
- **recording of retreatment with marketed talimogene laherparepvec during the registry study**

Statistical Considerations:

The statistical reporting of the safety endpoints and overall survival will be entirely descriptive, with no formal statistical testing performed.

Long-term safety as assessed by subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest, that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial, will be summarized.

In addition, **use of anti-cancer therapy for tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial and retreatment with marketed talimogene laherparepvec for approved indication** will be summarized.

For a full description of statistical analysis methods, refer to Section 10.

Sponsor: Amgen, Inc.

Data Elements Standards: Version 4.0, 31 October 2013

Study Glossary

Abbreviation or Term	Definition/Explanation
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EDC	electronic data capture
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
OS	overall survival
Parent Study	an Amgen or BioVEX-sponsored clinical trial in which the subject received at least one dose of talimogene laherparepvec
PT	preferred term
Registry	A list of subjects/patients presenting with the same characteristic(s). This/these characteristic(s) may be a disease or an outcome (disease registry) or a specific exposure (exposure or drug registry). Both types of registries, which only differ by the type of subject/patient data of interest, may collect a battery of information using standardized questionnaires in a prospective fashion.
SAEs	serious adverse events
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Example of source data include: subject identification.
USA	United States of America

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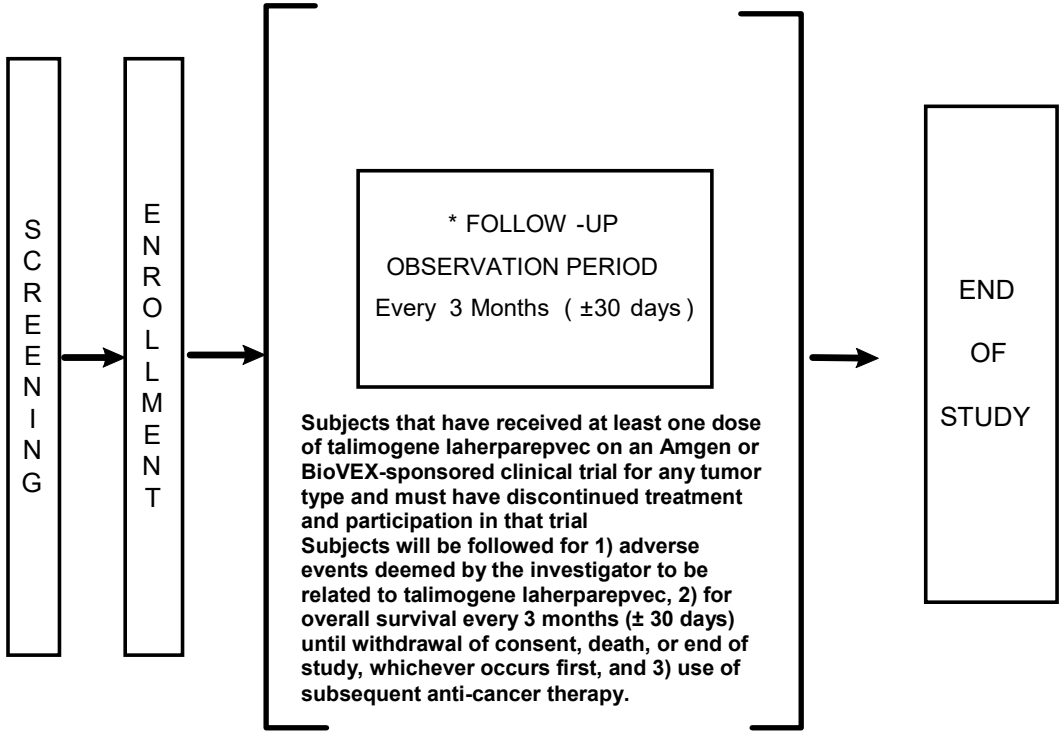
Study Design Schema



1. OBJECTIVES

1.1 Primary Objectives

The primary objectives are:

- To evaluate the long-term safety of talimogene laherparepvec
- To monitor subject overall survival
- **To monitor use of subsequent anti-cancer therapy, for the tumor indication in the prior Amgen or BioVEX-sponsored clinical trial, including retreatment with marketed talimogene laherparepvec for approved indication in subjects previously enrolled in Amgen or BioVEX-sponsored talimogene laherparepvec clinical trials**

2. RATIONALE and HYPOTHESES

2.1 Rationale

The purpose of this observational registry study is to monitor subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** for overall survival and long-term safety, as requested by the regulatory authorities. Subjects enrolled in the registry study will be contacted every 3 months (± **30** days) to assess long-term safety,survival data, **and use of subsequent anti-cancer therapy**. The minimum schedule of safety assessments for monitoring subjects is included in Table 1. The data collected by this registry study will provide information to better characterize the long-term effects of subjects that have received talimogene laherparepvec.

2.2 Hypotheses

A formal hypothesis will not be tested in this study. The goal of this observational registry study is to evaluate the overall survival, **use of subsequent anti-cancer therapy,** and the long-term safety of subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type**.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an international, multicenter, strictly observational registry program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or Bio**VEX**-sponsored clinical trial and have ended **treatment and participation, including long-term follow-up (if applicable) in** that trial. No experimental intervention is involved. Thus, a subject will undergo clinical assessments and receive the standard of care treatment as determined by the subject's physician. Subjects who consent to and

are eligible to enroll in this registry study will be monitored 1) for adverse events deemed by the investigator to be related to **treatment with** talimogene laherparepvec, 2) for overall survival every 3 months (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first, **and 3) use of subsequent anti-cancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial.**

If retreatment with **marketed** talimogene laherparepvec **for approved indication** is indicated during participation in the registry study, a subject **will continue** participation in the study **and the retreatment will be reported**.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Subjects

Participants in this study shall be referred to as "subjects". The total number of subjects who will participate in the registry will be determined by the number of subjects who remain alive at the end of the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial in which they participated **for any tumor type** and who consent and are deemed eligible to participate in this registry study.

3.3 Number of Sites

The number of sites that participate in this study will depend on the number of sites that have participated in an Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type** and have subjects who meet the eligibility criteria listed in Section 4.

3.4 Estimated Study Duration

3.4.1 Study Duration for Subjects

Duration of the study will vary for each subject. Subjects who end talimogene laherparepvec treatment on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and who consent to and are deemed eligible for participation in this registry study will be monitored for 1) adverse events deemed by the investigator to be related to **treatment with** talimogene laherparepvec for 2) overall survival every 3 months (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first, **and 3) for use of anti-cancer therapy for specific tumor type indicated in prior**

Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial including retreatment with marketed talimogene laherparepvec for approved indication.

3.4.2 End of Study

The registry study will end when the sponsor (in consultation with the regulatory authorities) has determined that the collection of long-term safety and survival data are no longer necessary.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates, including the date of screening and the outcome of the screening process (eg, enrolled into study, reason for ineligibility).

Before any study activities begin, including data collection, the appropriate written informed consent**/assent** must be obtained (Section 11.1).

4.1 Inclusion Criteria

101 All subjects must provide informed consent prior to initiation of any study activities. **When the subject is legally too young to provide informed consent/assent, subject's legally acceptable representative must provide informed consent/assent based on local regulations and/or guidelines prior to initiation of any study activities**

102 All subjects must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and must have discontinued treatment **and participation, including long-term follow-up (if applicable) i**n that trial

4.2 Exclusion Criteria

201 Subjects currently receiving talimogene laherparepvec in **Amgen or BioVEX-sponsored clinical trial**

202 Subject currently participating, including for long-term follow-up (if applicable), in other Amgen-sponsored talimogene laherparepvec clinical trial.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent**/assent** form, and all other subject information and/or recruitment material, if applicable (see Section 11.1). All subjects **or subject's legally acceptable representatives (when the subject is legally too young)** must personally sign and date the informed consent**/assent** form before commencement of study-specific activities (ie, non-standard of care procedures).

A subject is considered enrolled once he/she **or subject's legally acceptable representative (when the subject is legally too young)** has signed the informed consent**/assent** form and when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and in the case report form (CRF).

For each subject who enters into the screening period for this study (defined as the point when the subject signs the informed consent**/assent** form) the subject identification number(s), including the parent study number(s), assigned during participation in the previous Amgen or BioVEX-sponsored clinical trial(s) in which he/she received talimogene laherparepvec will be used to identify the subject throughout this study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire study; it must not be changed after initial assignment **and after being retreated with marketed talimogene laherparepvec.**

6. TREATMENT PROCEDURES

This is a non-interventional, observational registry study, and thus no treatment procedures are mandated by the study.

6.1 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate medical and supportive care except for those listed in Section 6.2**.**

6.2 Excluded Treatments During Study Period

A subject **that has been retreated with marketed talimogene laherparepvec for approved indication will be eligible to continue participation in the registry**.

7. STUDY-RELATED ACTIVITIES

This registry is an international, multicenter, strictly observational program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for all tumor types** and have ended treatment **and participation, including long-term follow-up (if applicable) in** that trial. No clinic visits other than those routinely scheduled will be required and subjects will undergo clinical assessments and receive the standard of care treatment as determined by their physician.

7.1 Schedule of Assessments

The Schedule of Assessments for the study is summarized in Table 1.

Table 1. Schedule of Assessments

Assessments	Screening/Enrollment[a]	Follow-up Observation Period (Every 3 (± 30 days) Months)[b]
Informed Consent[c]	X	-
Review of Eligibility Criteria	X	-
Protocol History[d]	X	-
Adverse Events[e]	X	X
Survival Assessment[f]	-	X
Recording of subsequent anti-cancer therapy[g]	X	X
Recording of subsequent treatment with marketed talimogene laherparepvec[h]	X	**X**

[a] To be completed at the completion of participation in the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for all tumor types**.
[b] The first 3-month assessment should occur 3 months (± **30** days) after the last study visit/assessment, including any follow-up visits, in the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial. **Subjects must be consented to participate in the current study prior to first follow-up contact.** Assessments continue every 3 **months** (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first.
[c] **When the subject is legally too young to provide informed consent/assent, subject's legally acceptable representative must provide informed consent/assent based on local regulations and/or guidelines prior to initiation of any study activities.**
[d] Recording of protocol history including the protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type**.
[e] Adverse events deemed by the investigator to be related to **treatment with** talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial. Adverse events that occur within 30 days of last dose of talimogene laherparepvec on the previous Amgen **and/**or BioVEX-sponsored clinical trial **or during long-term follow-up** should be recorded/reported under that trial, not in the registry study.
[f] Recording of survival status including date of contact and status (ie, alive or deceased and date/cause of death, if applicable)
[g] Recording of subsequent anti-cancer therapy **for specific tumor type indicated in the previous Amgen or BioVEX-sponsored clinical tria**l (including surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other anti-cancer therapy **and excluding retreatment with marketed talimogene laherparepvec**) that begins after the defined reporting period has ended on the previous clinical trial.
[h] **Recording of retreatment with marketed talimogene laherparepvec that was initiated after the end of previous talimogene laherparepvec clinical trial.**

7.2 General Study Assessments

A signed and dated IRB/IEC-approved informed consent**/assent** must be obtained before any study-specific assessments are performed. **If the subject is too young to provide informed consent/assent, subject's legally acceptable representative has to provide written assent based on local regulations and/or guidelines before any study-specific assessments are performed.** Assessments that are part of routine care are not considered study-specific and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

The Schedule of Assessments (Table 1) represents the core assessments to monitor any clinical manifestations related to the use of talimogene laherparepvec and to routinely assess survival.

7.2.1 Screening and Enrollment

The following assessments are to be completed during the screening/enrollment period at time points designated in the Schedule of Assessments (Table 1):

- Confirmation that the Informed Consent**/Assent** Form has been signed
- Review of inclusion and exclusion criteria
- Recording of protocol history including:
  - protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type**
- Recording of subsequent anti-cancer therapy, including **tumor-specific** surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other anti-cancer therapy **for indicated tumor in the previous Amgen or BioVEX-sponsored clinical trial and excluding retreatment with marketed talimogene laherparepvec**, that begins after the defined reporting period has ended on the previous talimogene laherparepvec clinical trial. **Retreatment with marketed talimogene laherparepvec for approved indication is reported separately.** Data to include:
  - type of therapy
  - start and stop dates
  - reason for cessation of therapy
- **Recording of subsequent retreatment with marketed talimogene laherparepvec after end of previous talimogene laherparepvec clinical trial. Data to include:**
  - **indication for retreatment with marketed talimogene laherparepvec**
  - **start and stop dates**
  - **reason for cessation of therapy**

- Recording of adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial

  Note: Adverse events that occur during participation on the previous Amgen or BioVEX-sponsored clinical trial should be recorded/reported under that trial, not in the registry study.

7.2.2 Follow-up Observation Period/End of Study

The following assessments are to be completed, via phone or clinic visit, every 3 months (± **30** days) during the follow-up observation period until withdrawal of consent, death, or end of study, whichever occurs first:

- Recording of subsequent anti-cancer therapy **during the registry study**, including **tumor-specific** surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other anti-cancer therapy **and excluding retreatment with marketed talimogene laherparepvec, for indicated tumor in the previous Amgen or BioVEX-sponsored clinical trial. Retreatment with marketed talimogene laherparepvec for approved indication is reported separately.** Data to include:
  - type of therapy
  - start and stop dates
  - reason for cessation of therapy
- **Recording of subsequent retreatment with marketed talimogene laherparepvec during the registry study. Data to include:**
  - **indication for retreatment with marketed talimogene laherparepvec**
  - **start and stop dates**
  - **reason for cessation of therapy**
- Recording of adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec **that occurred during the registry study**
- Recording of survival status including date of contact and status (ie, alive or deceased and date/cause of death, if applicable) **during the registry study**

8. WITHDRAWAL FROM ASSESSMENTS AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue protocol assessments at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from protocol assessments and must discuss with the subject the options

for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol assessments, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

If retreatment with marketed talimogene laherparepvec for approved indication is indicated during participation in the registry study a subject will be eligible to continue participation in the registry study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from protocol assessments or the study as a whole at any time prior to study completion.

8.3 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- start of retreatment with talimogene laherparepvec **in Amgen or BioVEX-sponsored clinical trial**
- decision by sponsor
- **participation in other Amgen-sponsored clinical trial**
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the

investigator or reported by the subject **as defined in the study protocol** are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

It is the investigator's responsibility to evaluate if an adverse event is related to an Amgen product prior to reporting the event to Amgen. **Only talimogene laherparepvec treatment-related events will be reported in this study.** The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial through end of study and are deemed by the investigator to be related to **the treatment with**

talimogene laherparepvec are reported using the applicable CRF (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- dates of onset and resolution (if resolved),
- severity [and/or toxicity per protocol],
- assessment of relatedness to talimogene laherparepvec, and
- action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version **4**.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to **the treatment with** talimogene laherparepvec. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the talimogene laherparepvec"?

If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Adverse Event Summary CRF. The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial through end of study and are deemed by the investigator to be related to talimogene laherparepvec are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the **Serious Adverse Event Report Form**. See Appendix B for a sample of the Serious Adverse Event Report Form.

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to

Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs in compliance with all reporting requirements according to local regulations and Good Clinical Practice.

The investigator is to notify the appropriate IRB of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

10. STATISTICAL CONSIDERATIONS

The statistical reporting of the safety endpoints and overall survival will be entirely descriptive (summary statistics), with no formal statistical testing performed.

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

- Long-term safety as assessed by subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial will be summarized. **Treatment-related adverse events during the retreatment period with marketed talimogene laherparepvec and up to 30 days after the discontinuation of treatment will be reported separately.**
- Survival status: Time to death will be calculated from the first dose of talimogene laherparepvec from the earliest parent study.
- **Use of subsequent anti-cancer therapy for indicated tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial will be summarized.**

10.1.2 Analysis Sets

Safety Analysis Set

Subjects who received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type** and have ended **participation in** that trial, and have been enrolled in this study.

10.1.3 Covariates and Subgroups

The following baseline covariates may be used to examine key safety endpoints or overall survival in the subgroups:

- Sex (male vs female)
- Age (< 50 vs ≥ 50 years, < 65 vs ≥ 65 years, < 75 vs ≥ 75 years)
- Race (white vs other)
- Parent study/ies (previous talimogene laherparepvec Amgen or BioVEX-sponsored clinical trial)
- **Tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Subsequent anti-cancer therapy **for indicated tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Prior parent study Adverse Events (eg, grade 3-4, Serious Adverse Events)
- Prior parent study Events Of Interest
- Duration of parent study talimogene laherparepvec
- Reason for parent study treatment discontinuation (eg, Adverse Events action discontinuation vs other)
- **Subsequent treatment with marketed talimogene laherparepvec for approved indication, including indications, duration of treatment and reason for discontinuation**

10.2 Sample Size Considerations

The statistical reporting of the safety outcomes will be entirely descriptive (summary statistics), with no formal statistical testing performed. Thus, no sample size calculations are presented here.

10.3 Planned Analyses

10.3.1 Interim Analysis

No interim analysis is planned for this study. However, ad hoc analyses may be conducted before the planned primary analysis.

10.3.2 Primary Analysis

The objective of the primary analysis is to evaluate the long-term safety of talimogene laherparepvec and monitor overall survival. The primary analysis will be performed at the end of study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Assessments for safety will be conducted on the safety analysis set. Descriptive analyses and listings for the safety endpoints are planned. Categorical outcomes will be described using the frequency and percent. Continuous outcomes will be described

using the mean, median, standard deviation, minimum, and maximum. Adverse events will be coded with the most recent version of Medical Dictionary for Regulatory Activities and will be grouped by system organ class and preferred term (PT) within system organ class. If a subject experiences multiple events that map to a single adverse event, the greatest severity and strongest investigator assessment of relation to study drug will be assigned to the adverse event. Event severity will be graded using CTCAE version **4**.0.

10.4.2 Demographic and Baseline Characteristics Obtained From Parent Study

Summary statistics of the following demographic and baseline characteristics from the parent study will be tabulated using the Safety Analysis Set:

- Country (USA or rest of the world)
- Sex (male vs female)
- Age at enrollment in parent study (< 50 vs ≥ 50 years, < 65 vs ≥ 65 years, < 75 vs ≥ 75 years)
- Race (white vs other)
- Previous talimogene laherparepvec Amgen or BioVEX-sponsored clinical trial
- **Tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Subsequent anti-cancer therapy **for indicated tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Prior parent study Adverse Events (eg, grade 3-4 SAE)
- Prior parent study Events Of Interest
- Duration of parent study talimogene laherparepvec exposure
- Reason for parent study treatment discontinuation (eg, Adverse Event action discontinuation vs other)
- Line of therapy (1st line vs 2nd or greater)
- Disease stage (early vs late)

To evaluate consistency between the registry subset versus all subjects that initiated talimogene laherparepvec, side-by-side comparisons of population characteristics will be tabulated for each parent trial's overall population versus registry subset. The comparison may include the safety profile, such as a high-level summary of adverse events, events of interest, talimogene laherparepvec exposure, and reasons for discontinuation.

10.4.3 Safety Endpoints

The subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, **talimogene laherparepvec treatment-related** grade ≥ 3 adverse

events, serious adverse events, fatal adverse events, and adverse events of interest will be summarized. Events will be reported separately, if any, with an onset date within 30 days of the last dose of talimogene laherparepvec in the last parent study.

All treatment-related adverse events will be listed in by-patient data listings. Deaths and serious treatment- related adverse events will be presented in a listing.

Treatment-related adverse events during the retreatment period with marketed talimogene laherparepvec and up to 30 days after the discontinuation of retreatment will be assessed and reported separately as treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest.

Overall survival will be summarized descriptively. In addition, follow-up time on the registry study and subsequent anti-cancer therapy **for indicated tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial and** received after the subject signs informed consent will be summarized.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent**/assent** form is provided for the investigator to prepare the informed consent**/assent** document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent**/assent** document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the study, the investigator is responsible for obtaining written informed consent/**assent,** where applicable by local regulations, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific activities/assessments are conducted.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent/**assent** and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent/**assent** form is to be signed and personally dated by the subject and by the person who conducted the informed consent/**assent** discussion. The original signed informed consent/**assent** form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent/**assent** form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent/**assent** form to attest that informed consent/**assent** was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent/**assent** form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent/**assent** form must be received by Amgen before study can be executed.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent/**assent** document. The investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval /renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRFs demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not for submission to Amgen (eg, signed informed consent**/assent** forms, as applicable) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/Local country regulations/International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the subject's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator. The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, written agreement from the investigator must be obtained. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the contractual agreement. The investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- subject files containing completed CRF, informed consent forms, and subject identification list
- study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the IRB/IEC or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the contractual agreement with Amgen.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen clinical monitor is responsible for verifying the CRFs throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research. The clinical monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs in accordance with the local laws and regulations.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH/GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global R&D Compliance and Audit function (or designees). Inspection of site facilities and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH/GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. In addition, the data is reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit) and clarifying "other, specify" if data are provided (eg, race). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the protocol requirements for all assessments and data collection as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required assessments and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors Guidelines).

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The contractual agreement

between the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

13. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version **4**.0 will be used for adverse event grading. The CTCAE version **4**.0 is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix B. Sample Serious Adverse Event Report Form

Project ID: 20120139 | AMGEN | Safety Reporting Form — Primary Data Collection | Date of Report:

Fax reports to: Amgen Local Office 1-805-480-9205

1. Indicate event type: ☐ AE/Other safety finding ☐ AE/Other safety finding with Product Complaint ☐ Product Complaint only

2. Vendor Contact Details

name	phone	fax
address		
city	state/province	
postal code	country	

3. Reporter ID

Name or ID	phone	fax
address		
city	state/province	
postal code	country	

4. HCP Contact Details (if other than reporter)

name		
country		
address		
city	state/province	postal code
phone	fax	

5. Patient

Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
	☐ F ☐ M		☐ Yes ☐ No

Weight	Height	Race	Is patient also reporter?
☐ lbs ☐ kg	☐ in ☐ cm		☐ Yes ☐ No

6. Medical History (include primary diagnosis)

7. Suspect Product Information (include dosing details)

Product: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Freq

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial size

8. AE, other safety finding, or product complaint information — HCP ONLY

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐Yes ☐No; Hospitalization Prolonged? ☐Yes ☐No; Admitting dx (provide discharge summary); Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=Drug withdrawn (date outcome)	Outcome: 1=resolved; 2=resolved w/ sequelae; 3=resolving	Severity: 1=mild; 2=moderate; 3=severe	Relationship to Product/ Device: Is there a reasonable possibility that this event may have been caused by the Product / Device? Product	Device
								Y N	Y N
								Y N	Y N
								Y N	Y N

9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

Reporter Signature: Page 1 of

The data provided by you will be transferred as a report to Global Safety at Amgen Inc. (USA) and will be exclusively used for safety and quality purposes
For vendor surveys of Health Care Professionals

FORM-067756 Ver. #: 3.0 Effective date: 07-Jul-2014 Page 1 of 1 ADR Form Created: 21-May-2015

Amendment 3

Protocol Title: A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec in Amgen or BioVEX-Sponsored Clinical Trials

Amgen Protocol Number (Talimogene Laherparepvec) 20120139

Amendment Date: 18 November 2015

Rationale:

The protocol has been amended primarily to change protocol title so it is not limited to melanoma subjects but yet available to all subjects that receive talimogene laherparepvec regardless of tumor type. It has also been amended to include subjects requiring retreatment with marketed talimogene laherparepvec for any indication.

In addition, the following changes have been incorporated into the protocol:

- Add a primary objective to indicate the changes described above.
- Include an endpoint to record the use of subsequent anticancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial and retreatment with marketed talimogene laherparepvec for approved indication
- Revise the inclusion criteria to clarify that when a subject is legally too young to provide informed consent/assent, subject's legally acceptable representative must provide informed consent/assent based on local regulations and/or guidelines prior to initiation of any study activities.
- Revise the exclusion criteria to clarify subjects will not be excluded if they will receive talimogene laherparepvec during the study.
- Revise the schedule of assessments to indicate that subjects must be consented to participate in the study prior to first follow-up contact.
- Revise the schedule of assessments to include recording of retreatment with marketed talimogene laherparepvec that was initiated after the end of treatment in previous talimogene laherparepvec clinical trial.
- Revise the schedule of assessments to clarify that when the subject is legally too young to provide informed consent/assent, subject's legally acceptable representative must provide informed consent/assent based on local regulations and/or guidelines prior to initiation of any study activities.
- Revise the window of follow-up visits from ± 15 to ± 30 days to align with the 20110266 study.

- Revise informed consent to include assent for minors.
- Update reporting procedures for adverse events and serious adverse events.
- Revise reasons for removal from the study.

Description of Change:

Section: Title

Replace:

A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects ~~With Melanoma~~ Who Previously Received Talimogene Laherparepvec

With:

A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec **in Amgen or BioVEX-Sponsored Clinical Trials**

Section: Global

Replace:

~~melanoma~~

With:

any tumor type

Section: Global

Replace:

~~Non-study~~

With:

marketed

Section: Header

Replace:

Talimogene Laherparapvec, 20120139, ~~25 February 2014~~

With:

Talimogene Laherparapvec, 20120139, **18 November 2015**

Section: Protocol Date

Add:

Amendment 3 Date	**18 November 2015**

Section: Cover Page

Replace:

Key Sponsor Contact(s):	PPD ~~PhD,~~ MD Clinical Research ~~Senior~~ Medical ~~Scientist~~ One Amgen Center Drive Thousand Oaks, CA 91320-1799 Telephone: PPD Email address: PPD PPD Clinical Research Study Manager 34 Commerce Way Woburn, MA 01801 Telephone: PPD Email address: PPD
Date:	01 May 2008
Amendment 1 Date:	11 February 2010
Amendment 2 Date:	25 February 2014

With:

Key Sponsor Contact(s):	PPD **MD, PhD** Clinical Research Medical **Director** One Amgen Center Drive Thousand Oaks, CA 91320-1799 Telephone: PPD Email address: PPD PPD Clinical Research Study Manager 34 Commerce Way Woburn, MA 01801 **Telephone:** PPD Email address: PPD
Date:	01 May 2008
Amendment 1 Date:	11 February 2010
Amendment 2 Date:	25 February 2014
Amendment 3 Date:	**18 November 2015**

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled **A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects ~~With Melanoma~~ Who Previously Received Talimogene Laherparepvec**, dated 25 February 2014**,** and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled **A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects Who Previously Received Talimogene Laherparepvec in Amgen or BioVEX-Sponsored Clinical Trials**, dated **18 November 2015,** and agree to abide by all provisions set forth therein.

Section: Protocol Synopsis, Indication

Replace:

~~Melanoma~~

With:

Any tumor type eligible for treatment with talimogene laherparepvec in Amgen or BioVEX-sponsored clinical trial

Section: Protocol Synopsis, Primary Objectives

Add:

To monitor use of subsequent anticancer therapy, for the tumor indication in the prior Amgen or BioVEX-sponsored clinical trial, including retreatment with marketed talimogene laherparepvec in subjects previously enrolled in Amgen or BioVEX-sponsored clinical trials

Section: Protocol Synopsis, Hypothesis

Add:

A formal hypothesis will not be tested in this study. The goal of this observational registry study is to evaluate the overall survival, **use of subsequent anticancer therapy,** and the long-term safety of subjects who have received at least one dose of

talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type**.

Section: Protocol Synopsis, Study Endpoint(s)

Add:

- Long-term safety as assessed by subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest, that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **will be summarized. Talimogene laherparepvec treatment-related adverse events during the retreatment period with marketed talimogene laherparepvec and up to 30 days after the discontinuation of treatment will be reported separately.**

Section: Protocol Synopsis, Study Endpoint(s)

Replace:

- Overall survival

With:

- **Survival status.**

Section: Protocol Synopsis, Study Endpoint(s)

Add:

Use of subsequent anticancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial including retreatment with marketed talimogene laherparepvec for approved indication.

Section: Protocol Synopsis, Study Design

Replace:

This is an international, multicenter, strictly observational registry program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial and have ~~permanently~~ ended treatment ~~on~~ that trial. No experimental intervention is involved. Thus, a subject will undergo clinical assessments and receive the standard of care treatment as determined by the subject's physician.

Subjects who consent to and are eligible to enroll in this registry study will be monitored 1) for adverse events deemed by the investigator to be related to talimogene laherparepvec ~~and~~ 2) for overall survival every 3 months (± ~~15~~ days) until withdrawal of consent, death, or end of study, whichever occurs first.

If retreatment with talimogene laherparepvec is indicated during participation in the registry study ~~(as applicable, based on the parent study in which the subject participated)~~ a subject ~~must end~~ participat~~ion~~ in the registry study ~~prior to starting talimogene laherparepvec. The subject may be re-consented to participate in the registry study once talimogene laherparepvec has been permanently discontinued and may be enrolled into the registry study if he/she meets the eligibility criteria listed in Section 4.~~

With:

This is an international, multicenter, strictly observational registry program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and have ended treatment **and participation, including long term follow-up, in** that trial. No experimental intervention is involved. Thus, a subject will undergo clinical assessments and receive the standard of care treatment as determined by the subject's physician. Subjects who consent to and are eligible to enroll in this registry study will be monitored 1) for adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec, 2) for overall survival every 3 months (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first, **and 3) use of anti-cancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial including retreatment with marketed talimogene laherparepvec for approved indication.**

If retreatment with **marketed** talimogene laherparepvec **for approved indication** is indicated during participation in the registry study, a subject **will continue** to participat**e** in the registry study **and the retreatment will be reported**.

Section: Protocol Synopsis, Sample Size

Add:

The total number of subjects who will participate in the registry study will be determined by the number of subjects who remain alive at the end of the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial in which they participated **for any tumor type** and who consent to and are deemed eligible to participate in this registry study.

Section: Protocol Synopsis, Key Inclusion Criteria

Replace:

Subject must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial and must have ~~permanently~~ discontinued treatment ~~on~~ that trial.

With:

Subject must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and must have discontinued treatment **and follow-up in** that trial. **Subjects that have been retreated with marketed talimogene laherparepvec for approved indication are also eligible to participate in the study**.

Section: Protocol Synopsis, Key Exclusion Criteria

Replace:

Subject must not be currently receiving ~~or planning to receive~~ talimogene laherparepvec ~~in the 30 days following enrollment into the registry study~~.

With:

Subject must not be currently receiving talimogene laherparepvec **on an Amgen or BioVEX-sponsored clinical trial**. **Subject currently participating, including for long-term follow up, in other Amgen -sponsored talimogene laherparepvec clinical trial.**

Section: Protocol Synopsis, Assessments

Replace:

Screening/Enrollment:

The following assessments will be performed during the screening/enrollment period:

- confirmation that the informed consent form has been signed
- review of inclusion and exclusion criteria
- recording of protocol history (ie, protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial)
- recording of subsequent anticancer ~~melanoma~~ therapy that begins after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial
- recording of adverse events deemed by the investigator to be related to talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial

Follow-up Observation Period/End of Study:

The following assessments will be performed via phone or clinic visit every 3 months (± ~~15~~ days) during the follow-up observation period until withdrawal of consent, death, or end of study, whichever occurs first:

- recording of subsequent anticancer ~~melanoma~~ therapy
- ~~recording of adverse events deemed by the investigator to be related to talimogene laherparepvec~~
- ~~recording of survival status including date of contact, status (ie, alive or deceased and date/cause of death, if applicable)~~

With:

Screening/Enrollment:

The following assessments will be performed during the screening/enrollment period:

- confirmation that the informed consent/**assent** form has been signed
- review of inclusion and exclusion criteria
- recording of protocol history (ie, protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial)
- recording of subsequent anticancer therapy **for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial and** that begins after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **and prior to enrollment in the registry study**

- **recording of retreatment with marketed talimogene laherparepvec after end of previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial and prior to enrollment in the registry study**
- recording of adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial

Follow-up Observation Period/End of Study:

The following assessments will be performed via phone or clinic visit every 3 months (± **30** days) during the follow-up observation period until withdrawal of consent, death, or end of study, whichever occurs first:

- **recording of adverse events deemed by the investigator to be related to the treatment with talimogene laherparepvec during the registry study**
- **recording of survival status including date of contact, status (ie, alive or deceased and date/cause of death, if applicable) during the registry study**
- recording of subsequent anticancer therapy **for tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial during the registry study**
- **recording of retreatment with marketed talimogene laherparepvec during the registry study**

Section: Protocol Synopsis, Statistical Considerations

Replace:

The statistical reporting of the safety endpoints and overall survival will be entirely descriptive, with no formal statistical testing performed.

Long-term safety as assessed by subject incidence of all treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest, that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial, will be summarized.

In addition, ~~overall survival~~ will be summarized.

With:

The statistical reporting of the safety endpoints and overall survival will be entirely descriptive, with no formal statistical testing performed.

Long-term safety as assessed by subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest, that begin after the

defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial, will be summarized.

In addition, **use of anticancer therapy for tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial and retreatment with marketed talimogene laherparepvec for approved indication** will be summarized.

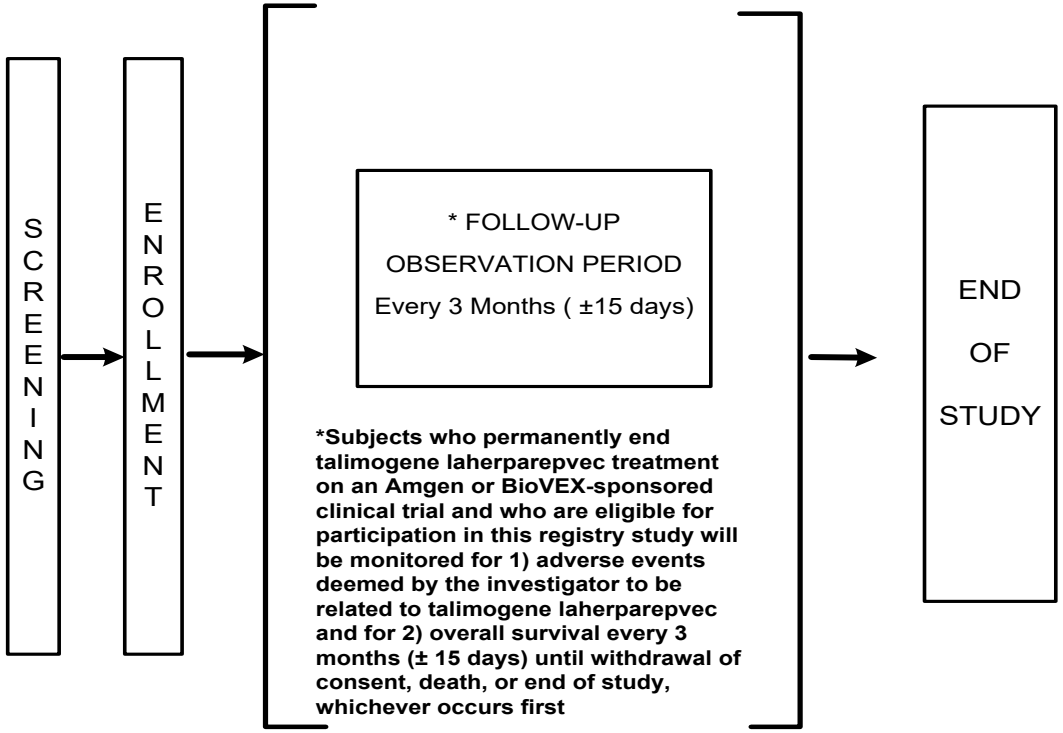
Section: Study Glossary

Delete:

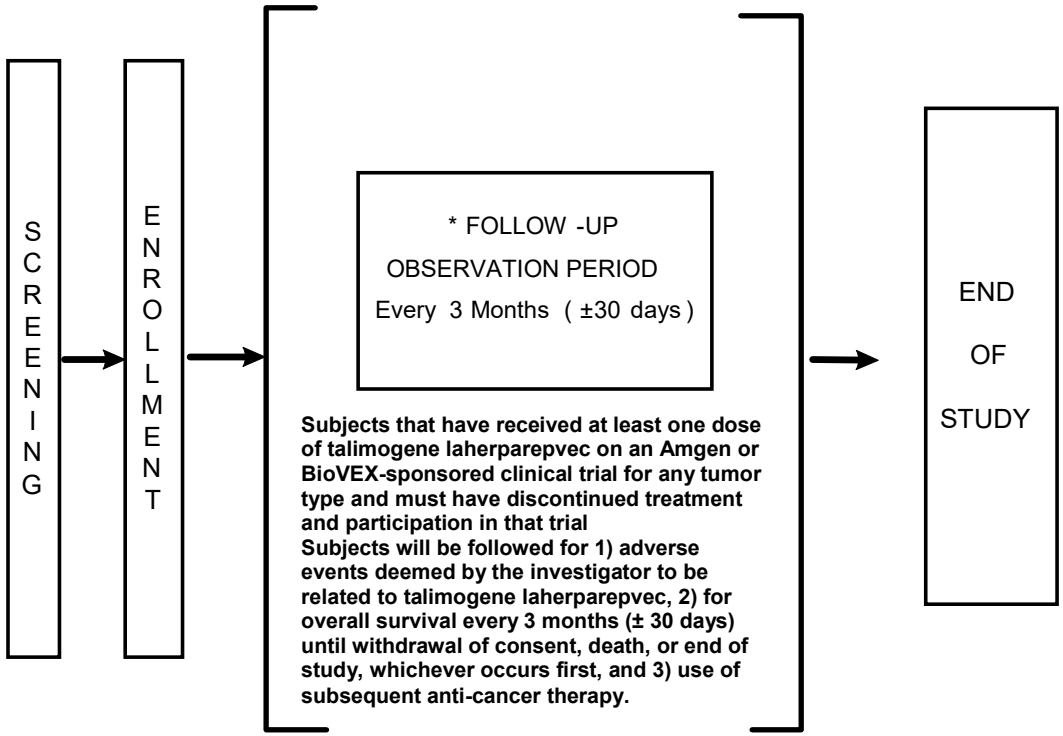
Abbreviation or Term	Definition/Explanation
CRF	case report form
~~CSR~~	~~Clinical Study Report~~
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EDC	electronic data capture
~~FDA~~	~~Food and Drug Administration~~
GCP	Good Clinical Practice
~~GM-CSF~~	~~granulocyte macrophage colony-stimulating factor~~
~~HR~~	~~hazard ratio~~
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
~~MedDRA~~	~~Medical Dictionary for Regulatory Activities~~
OS	overall survival
Parent Study	an Amgen or BioVEX-sponsored clinical trial in which the subject received at least one dose of talimogene laherparepvec
PT	preferred term
~~RAC~~	~~Recombinant DNA Advisory Committee~~

Section: Study Design Schema

Replace:



With:



Section: 1.1 Primary Objectives

Add:

To monitor use of subsequent anticancer therapy, for the tumor indication in the prior Amgen or BioVEX-sponsored clinical trial, including retreatment with marketed talimogene laherparepvec for approved indication in subjects previously enrolled in Amgen or BioVEX-sponsored talimogene laherparepvec clinical trials

Section: 2.1 Rationale

Replace:

The purpose of this observational registry study is to monitor subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX sponsored clinical trial for overall survival and long-term safety, as requested by the regulatory authorities. Subjects enrolled in the registry study will be contacted every 3 months (± ~~15~~ days) to assess long-term safety ~~and~~ survival data.

With:

The purpose of this observational registry study is to monitor subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** for overall survival and long-term safety, as requested by the regulatory authorities. Subjects enrolled in the registry study will be contacted every 3 months (± **30** days) to assess long-term safety**,** survival data, **and use of subsequent anti-cancer therapy**.

Section: 2.2. Hypotheses

Add:

A formal hypothesis will not be tested in this study. The goal of this observational registry study is to evaluate the overall survival**, use of subsequent anticancer therapy,** and the long-term safety of subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type**.

Section: 3.1 Study Design

Replace:

This is an international, multicenter, strictly observational registry program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or Bio~~vex~~-sponsored clinical trial and have ~~permanently~~ ended treatment ~~on~~ that trial. No experimental intervention is involved. Thus, a subject will undergo clinical assessments and receive the standard of care treatment as determined by the subject's physician. Subjects who consent to and are eligible to enroll in this registry study will be monitored 1) for adverse events deemed by the investigator to be related to talimogene laherparepvec ~~and~~ 2) for overall survival every 3 months (± ~~15~~ days) until withdrawal of consent, death, or end of study, whichever occurs first.

If retreatment with talimogene laherparepvec is indicated during participation in the registry study ~~(as applicable, based on the parent study in which the subject participated)~~ a subject ~~must end~~ participat~~ion~~ in the registry study ~~prior to starting talimogene laherparepvec. The subject may be re-consented to participate in the registry study once talimogene laherparepvec has been permanently discontinued and may be enrolled into the registry study if he/she meets the eligibility criteria listed in Section 4.~~

With:

This is an international, multicenter, strictly observational registry program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or Bio**VEX**-sponsored clinical trial and have ended treatment **and participation, including long-term follow-up (if applicable) in** that trial. No experimental intervention is involved. Thus, a subject will undergo clinical assessments and receive the standard of care treatment as determined by the subject's physician. Subjects who consent to and are eligible to enroll in this registry study will be monitored 1) for adverse events deemed by the investigator to be related to **treatment with** talimogene laherparepvec, 2) for overall survival every 3 months (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first, **and 3) use of anti-cancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial.**

If retreatment with **marketed** talimogene laherparepvec **for approved indication** is indicated during participation in the registry study**,** a subject **will continue participation** in the study **and the retreatment will be reported**.

Section: 3.2 Number of Subjects

Add:

Participants in this study shall be referred to as “subjects”. The total number of subjects who will participate in the registry will be determined by the number of subjects who remain alive at the end of the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial in which they participated **for any tumor type** and who consent and are deemed eligible to participate in this registry study.

Section: 3.3 Number of Sites

Add:

The number of sites that participate in this study will depend on the number of sites that have participated in an Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type** and have subjects who meet the eligibility criteria listed in Section 4.

Section: 3.4.1 Study Duration of Subjects

Replace:

Duration of the study will vary for each subject. Subjects who ~~permanently~~ end talimogene laherparepvec treatment on an Amgen or BioVEX-sponsored clinical trial and who consent to and are deemed eligible for participation in this registry study will be monitored for 1) adverse events deemed by the investigator to be related to talimogene laherparepvec ~~and~~ for 2) overall survival every 3 months (± ~~15~~ days) until withdrawal of consent, death, or end of study, whichever occurs first.

With:

Duration of the study will vary for each subject. Subjects who end talimogene laherparepvec treatment on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and who consent to and are deemed eligible for participation in this registry study will be monitored for 1) adverse events deemed by the investigator to be related to **treatment with** talimogene laherparepvec, for 2) overall survival every 3 months (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first,

and 3) for use of anticancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial including retreatment with marketed talimogene laherparepvec for approved indication.

Section: 4. Subject Eligibility

Add:

Before any study activities begin, including data collection, the appropriate written informed consent**/assent** must be obtained (Section 11.1).

Section: 4.1 Inclusion Criteria

Replace:

101 All subjects must provide informed consent prior to initiation of any study activities

102 All subjects must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial and must have ~~permanently~~ discontinued treatment on that trial

With:

101 All subjects must provide informed consent prior to initiation of any study activities. **When the subject is legally too young to provide informed consent/assent, subject's legally acceptable representative must provide informed consent/assent based on local regulations and/or guidelines prior to initiation of any study activities**

102 All subjects must have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for any tumor type** and must have discontinued treatment **and participation, including long-term follow up (if applicable) i**n that trial

Section: 4.2 Exclusion Criteria

Replace:

201 Subjects currently receiving ~~or planning to receive~~ talimogene laherparepvec in ~~the next 30 days~~

With:

201 Subjects currently receiving talimogene laherparepvec in **Amgen or BioVEX-sponsored clinical trial**

202 Subject currently participating, including for long-term follow up (if applicable), in other Amgen-sponsored talimogene laherparepvec clinical trial.

Section: 5 Subject Enrollment

Add:

Before subjects begin participation in any study-specific activities, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent**/assent** form, and all other subject information and/or recruitment material, if applicable (see Section 11.1). All subjects **or subject's legally acceptable representatives (when the subject is legally too young)** must personally sign and date the informed consent**/assent** form before commencement of study-specific activities (ie, non-standard of care procedures).

A subject is considered enrolled once he/she **or subject's legally acceptable representative (when the subject is legally too young)** has signed the informed consent**/assent** form and when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date in the subject's medical record and in the case report form (CRF).

For each subject who enters into the screening period for this study (defined as the point when the subject signs the informed consent**/assent** form) the subject identification number(s), including the parent study number(s), assigned during participation in the previous Amgen or BioVEX-sponsored clinical trial(s) in which he/she received talimogene laherparepvec will be used to identify the subject throughout this study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire study; it must not be changed after initial assignment **and after being retreated with marketed talimogene laherparepvec.**

Section: 6.2 Excluded Treatments During Study Period

Replace:

A subject ~~must end participation in this registry study prior to retreatment with talimogene laherparepvec. The subject may re-consent to participate in the registry study once talimogene laherparepvec treatment has been permanently discontinued and may be enrolled into the registry study if he/she meets the eligibility criteria listed in Section 4.~~

With:

A subject **that has been retreated with marketed talimogene laherparepvec for approved indication will be eligible to continue participation in the registry**.

Section: 7 Study Related Activities

Replace:

This registry is an international, multicenter, strictly observational program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial and have ~~permanently~~ ended treatment on that trial. No clinic visits other than those routinely scheduled will be required and subjects will undergo clinical assessments and receive the standard of care treatment as determined by their physician.

With:

This registry is an international, multicenter, strictly observational program for subjects who have received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored clinical trial **for all tumor types** and have ended treatment **and participation, including long-term follow up (if applicable) in** that trial. No clinic visits other than those routinely scheduled will be required and subjects will undergo clinical assessments and receive the standard of care treatment as determined by their physician.

Section: 7.1 Schedule of Assessments, Table 1

Replace:

Assessments	Screening/Enrollment [a]	Follow-up Observation Period (Every 3 (± ~~15~~ days) Months)[b]
Informed Consent	X	
Review of Eligibility Criteria	X	
Protocol History[c]	X	
Adverse Events [d]	X	X
Survival Assessment[e]		X
Recording of subsequent anticancer ~~melanoma~~ therapy[f]	X	X

With:

Assessments	Screening/Enrollment[a]	Follow-up Observation Period (Every 3 (± **30** days) Months)[b]
Informed Consent[c]	X	-
Review of Eligibility Criteria	X	-
Protocol History[d]	X	-
Adverse Events [e]	X	X
Survival Assessment[f]	-	X
Recording of subsequent anticancer therapy[g]	X	X
Recording of subsequent treatment with marketed talimogene laherparepvec[h]	**X**	**X**

Section: 7.1 Schedule of Assessments, footnotes

Replace:

~~a)~~ To be completed at the completion of participation in the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial.
~~b)~~ The first 3-month assessment should occur 3 months (± ~~15~~ days) after the last study visit/assessment, including any follow-up visits, in the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial. Assessments continue every 3 (± ~~15~~ days) months until withdrawal of consent, death, or end of study, whichever occurs first.
~~c)~~ Recording of protocol history including the protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial.
~~d)~~ Adverse events deemed by the investigator to be related to talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial. Adverse events that occur within 30 days of last dose of talimogene laherparepvec on the previous Amgen or BioVEX-sponsored clinical trial should be recorded/reported under that trial, not in the registry study.
~~e)~~ Recording of survival status including date of contact and status (ie, alive or deceased and date/cause of death, if applicable)
~~f)~~ Recording of subsequent anticancer ~~melanoma~~ therapy (including surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other systemic anticancer therapy) that begins after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial.

With:

[a] To be completed at the completion of participation in the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for all tumor types**.
[b] The first 3-month assessment should occur 3 months (± **30** days) after the last study visit/assessment, including any follow-up visits, in the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial. **Subjects must be consented to participate in the current study prior to first follow-up contact.** Assessments continue every 3 **months** (± **30** days) until withdrawal of consent, death, or end of study, whichever occurs first.
[c] **When the subject is legally too young to provide informed consent/assent, subject's legally acceptable representative must provide informed consent/assent based on local regulations and/or guidelines prior to initiation of any study activities.**
[d] Recording of protocol history including the protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type**.

[e] Adverse events deemed by the investigator to be related to **treatment with** talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial. Adverse events that occur within 30 days of last dose of talimogene laherparepvec on the previous Amgen **and/**or BioVEX-sponsored clinical trial **or during long-term follow-up** should be recorded/reported under that trial, not in the registry study.

[f] Recording of survival status including date of contact and status (ie, alive or deceased and date/cause of death, if applicable)

[g] Recording of subsequent anti-cancer therapy **for specific tumor type indicated in the previous Amgen or BioVEX-sponsored clinical trial** (including surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other anti-cancer therapy **and excluding retreatment with marketed talimogene laherparepvec**) that begins after the defined reporting period has ended on the previous clinical trial.

[h] **Recording of retreatment with marketed talimogene laherparepvec that was initiated after the end of previous talimogene laherparepvec clinical trial.**

Section: 7.2 General Study Assessments

Add:

A signed and dated IRB/IEC-approved informed consent**/assent** must be obtained before any study-specific assessments are performed. **If the subject is too young to provide informed consent/assent, subject's legally acceptable representative has to provide written assent based on local regulations and/or guidelines before any study-specific assessments are performed.** Assessments that are part of routine care are not considered study-specific and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

Section: 7.2.1 Screening and Enrollment

Replace:

The following assessments are to be completed during the screening/enrollment period at time points designated in the Schedule of Assessments (Table 1):

- Confirmation that the Informed Consent Form has been signed
- Review of inclusion and exclusion criteria
- Recording of protocol history including:
  - protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial
- Recording of subsequent anticancer ~~melanoma~~ therapy, including surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other ~~systemic~~ anticancer therapy, that begins after the defined reporting period has

ended on the previous ~~Amgen or BioVEX-sponsored~~ talimogene laherparepvec clinical trial. Data to include:

- type of therapy
- start and stop dates
- reason for cessation of therapy

- Recording of adverse events deemed by the investigator to be related to talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial

  Note: Adverse events that occur during participation on the previous Amgen or BioVEX-sponsored clinical trial should be recorded/reported under that trial, not in the registry study.

With:

The following assessments are to be completed during the screening/enrollment period at time points designated in the Schedule of Assessments (Table 1):

- Confirmation that the Informed Consent/**Assent** Form has been signed
- Review of inclusion and exclusion criteria
- Recording of protocol history including:
  - protocol number(s) and assigned subject identification number(s) from the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type**
- Recording of subsequent anticancer therapy, including **tumor-specific** surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other anticancer therapy **for indicated tumor in the previous Amgen or BioVEX-sponsored clinical trial and excluding retreatment with marketed talimogene laherparepvec**, that begins after the defined reporting period has ended on the previous talimogene laherparepvec clinical trial. **Retreatment with marketed talimogene laherparepvec for approved indication is reported separately.** Data to include:
  - type of therapy
  - start and stop dates
  - reason for cessation of therapy
- **Recording of subsequent retreatment with marketed talimogene laherparepvec after end of previous talimogene laherparepvec clinical trial. Data to include:**
  - **indication for retreatment with marketed talimogene laherparepvec**
  - **start and stop dates**
  - **reason for cessation of therapy**

- Recording of adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial

  Note: Adverse events that occur during participation on the previous Amgen or BioVEX-sponsored clinical trial should be recorded/reported under that trial, not in the registry study.

Section: 7.2.2 Follow-up Observation Period/End of Study

Replace:

The following assessments are to be completed, via phone or clinic visit, every 3 months (± ~~15~~ days) during the follow-up observation period until withdrawal of consent, death, or end of study, whichever occurs first:

- Recording of subsequent anticancer ~~melanoma~~ therapy, including surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other ~~systemic~~ anticancer therapy. Data to include:
  - type of therapy
  - start and stop dates
  - reason for cessation of therapy
- Recording of adverse events deemed by the investigator to be related to talimogene laherparepvec
- Recording of survival status including date of contact and status (ie, alive or deceased and date/cause of death, if applicable)

With:

The following assessments are to be completed, via phone or clinic visit, every 3 months (± **30** days) during the follow-up observation period until withdrawal of consent, death, or end of study, whichever occurs first:

- Recording of subsequent anticancer therapy **during the registry study**, including **tumor-specific** surgical procedures, radiotherapy, chemotherapy, biological therapy, immunotherapy, and/or other anticancer therapy **and excluding retreatment with marketed talimogene laherparepvec, for indicated tumor in the previous Amgen or BioVEX-sponsored clinical trial. Retreatment with marketed talimogene laherparepvec for approved indication is reported separately.** Data to include:
  - type of therapy
  - start and stop dates
  - reason for cessation of therapy

- **Recording of subsequent retreatment with marketed talimogene laherparepvec during the registry study. Data to include:**
  - **indication for retreatment with marketed talimogene laherparepvec**
  - **start and stop dates**
  - **reason for cessation of therapy**
- Recording of adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec **that occurred during the registry study**
- Recording of survival status including date of contact and status (ie, alive or deceased and date/cause of death, if applicable) **during the registry study**

Section: 8.1 Subjects' Decision to Withdraw

Add:

If retreatment with marketed talimogene laherparepvec for approved indication is indicated during participation in the registry study a subject will be eligible to continue participation in the registry study.

Section: 8.3 Reasons for Removal From Study

Add:

Reasons for removal of a subject from the study are:

- start of retreatment with talimogene laherparepvec **in Amgen or BioVEX-sponsored clinical trial**
- decision by sponsor
- **participation in other Amgen-sponsored clinical trial**
- withdrawal of consent from study
- death
- lost to follow-up

Section: 9.1.1 Definition of Adverse Events

Add:

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject **as defined in the study protocol** are recorded in the subject's medical record.

Section: 9.1.2 Definition of Serious Adverse Events

Delete:

A serious adverse event is defined as an adverse event that meets at least 1 of the following ~~serious~~ criteria:

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

Add:

It is the investigator's responsibility to evaluate if an adverse event is related to an Amgen product prior to reporting the event to Amgen. **Only talimogene laherparepvec treatment-related events will be reported in this study.** The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial through end of study and are deemed by the investigator to be related to **the treatment with** talimogene laherparepvec are reported using the applicable CRF (eg, Adverse Event Summary).

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

Replace:

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version ~~3~~.0.

With:

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version **4**.0.

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

Add:

The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to **the treatment with** talimogene laherparepvec.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events

Replace:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial through end of study and are deemed by the investigator to be related to talimogene laherparepvec are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events deemed by the investigator to be related to talimogene laherparepvec must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the ~~applicable CRF~~.

~~If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event.~~ See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. ~~For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the electronic Serious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.~~

With:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial through end of study and are deemed by the investigator to be related to talimogene laherparepvec are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events deemed by the investigator to be related to **the treatment with** talimogene laherparepvec must be submitted to Amgen

within 24 hours following the investigator's knowledge of the event via the **Serious Adverse Event Report Form.** See Appendix B for a sample of the Serious Adverse Event Report Form.

Section: 10.1.1 Study Endpoint(s)

Add:

- Long-term safety as assessed by subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest, that begin after the defined reporting period has ended on the previous Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial will be summarized. **Treatment-related adverse events during the retreatment period with marketed talimogene laherparepvec and up to 30 days after the discontinuation of treatment will be reported separately.**
- Survival status: Time to death will be calculated from the first dose of talimogene laherparepvec from the earliest parent study.
- **Use of subsequent anticancer therapy for specific tumor type indicated in prior Amgen or BioVEX-sponsored clinical trial will be summarized.**

Section: 10.1.2 Analysis Sets

Replace:

Subjects who received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial and have ~~permanently~~ ended ~~treatment on~~ participation in that trial, and have been enrolled in this study.

With:

Subjects who received at least one dose of talimogene laherparepvec on an Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial **for any tumor type** and have ended **participation in** that trial, and have been enrolled in this study.

Section: 10.1.3 Covariates and Subgroups

Replace:

The following baseline covariates may be used to examine key safety endpoints or overall survival in the subgroups:

- Sex (male vs female)
- Age (< 50 vs ≥ 50 years, < 65 vs ≥ 65 years, < 75 vs ≥ 75 years)
- Race (white vs other)
- Parent study/ies (previous talimogene laherparepvec Amgen or BioVEX-sponsored clinical trial
- Subsequent anticancer ~~melanoma~~ therapy
- Prior parent study ~~Treatment Emergent~~ Adverse Events (eg, grade 3-4, Serious Adverse Events)
- ~~Prior parent study related Treatment Emergent Adverse Events (eg, grade 3-4, Serious Adverse Events)~~
- Prior parent study Events Of Interest
- Duration of parent study talimogene laherparepvec
- Reason for parent study treatment discontinuation (eg, ~~Treatment Emergent~~ Adverse Events action discontinuation vs other)

With:

The following baseline covariates may be used to examine key safety endpoints or overall survival in the subgroups:

- Sex (male vs female)
- Age (< 50 vs ≥ 50 years, < 65 vs ≥ 65 years, < 75 vs ≥ 75 years)
- Race (white vs other)
- Parent study/ies (previous talimogene laherparepvec Amgen or BioVEX-sponsored clinical trial)
- **Tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Subsequent anticancer therapy **for indicated tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Prior parent study Adverse Events (eg, grade 3-4, Serious Adverse Events)
- Prior parent study Events Of Interest
- Duration of parent study talimogene laherparepvec
- Reason for parent study treatment discontinuation (eg, Adverse Events action discontinuation vs other)
- **Subsequent treatment with marketed talimogene laherparepvec, for approved indication, including indications, duration of treatment and reason for discontinuation**

Section: 10.4.1 General Considerations

Replace:

If a subject experiences multiple events that map to a single adverse event, the greatest severity and strongest investigator assessment of relation to study drug will be assigned to the adverse event. Event severity will be graded using CTCAE version ~~3~~.0

With:

If a subject experiences multiple events that map to a single adverse event, the greatest severity and strongest investigator assessment of relation to study drug will be assigned to the adverse event. Event severity will be graded using CTCAE version **4**.0

Section: 10.4.2 Demographics and Baseline Characteristics From Parent Study

Add:

Demographics and Baseline Characteristics **Obtained** from Parent Study

Section: 10.4.2 Demographics and Baseline Characteristics Obtained from Parent Study

Replace:

Summary statistics of the following demographic and baseline characteristics from the parent study will be tabulated using the Safety Analysis Set:

- Country (USA or rest of the world)
- Sex (male vs female)
- Age at enrollment in parent study (< 50 vs ≥ 50 years, < 65 vs ≥ 65 years, < 75 vs ≥ 75 years)
- Race (white vs other)
- Previous talimogene laherparepvec Amgen or BioVEX-sponsored clinical trial
- Subsequent anticancer ~~melanoma~~ therapy
- Prior parent study ~~Treatment Emergent~~ Adverse Events (eg, grade 3-4 SAE)
- ~~Prior parent study related Treatment Emergent Adverse Events (eg, grade 3-4, SAE)~~
- Prior parent study Events Of Interest
- Duration of parent study talimogene laherparepvec exposure

- Reason for parent study treatment discontinuation (eg, ~~Treatment Emergent~~ Adverse Event action discontinuation vs other)
- Line of therapy (1st line vs 2nd or greater)
- Disease stage (early vs late)

With:

Summary statistics of the following demographic and baseline characteristics from the parent study will be tabulated using the Safety Analysis Set:

- Country (USA or rest of the world)
- Sex (male vs female)
- Age at enrollment in parent study (< 50 vs ≥ 50 years, < 65 vs ≥ 65 years, < 75 vs ≥ 75 years)
- Race (white vs other)
- Previous talimogene laherparepvec Amgen or BioVEX-sponsored clinical trial
- **Tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Subsequent anticancer therapy **for indicated tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial**
- Prior parent study Adverse Events (eg, grade 3-4 SAE)
- Prior parent study Events Of Interest
- Duration of parent study talimogene laherparepvec exposure
- Reason for parent study treatment discontinuation (eg, Adverse Event action discontinuation vs other)
- Line of therapy (1st line vs 2nd or greater)
- Disease stage (early vs late)

Section: 10.4.3 Safety Endpoints

Replace:

The subject incidence of all treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest will be summarized. Events will be reported separately, if any, with an onset date within 30 days of the last dose of talimogene laherparepvec in the last parent study.

All treatment-related adverse events will be listed in by-patient data listings. Deaths and serious treatment- related adverse events will be presented in a listing.

Overall survival will be summarized descriptively. In addition, follow-up time on the registry study and subsequent anti-cancer ~~melanoma~~ therapy and received after the subject signs informed consent will be summarized.

With:

The subject incidence of all **talimogene laherparepvec** treatment-related adverse events of any grade, **talimogene laherparepvec treatment-related** grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest will be summarized. Events will be reported separately, if any, with an onset date within 30 days of the last dose of talimogene laherparepvec in the last parent study.

All treatment-related adverse events will be listed in by-patient data listings. Deaths and serious treatment- related adverse events will be presented in a listing.
Treatment-related adverse events during the retreatment period with marketed talimogene laherparepvec and up to 30 days after the discontinuation of retreatment will be assessed and reported separately as treatment-related adverse events of any grade, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, and adverse events of interest.

Overall survival will be summarized descriptively. In addition, follow-up time on the registry study and subsequent anti-cancer therapy **for indicated tumor type in prior Amgen or BioVEX-sponsored talimogene laherparepvec clinical trial and** received after the subject signs informed consent will be summarized.

Section: 11.1 Informed Consent

Add:

An initial sample informed consent**/assent** form is provided for the investigator to prepare the informed consent**/assen**t document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent**/assent** document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the study, the investigator is responsible for obtaining written informed consent**/assent**, where applicable by local regulations, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific activities/assessments are conducted.

The acquisition of informed consent/**assent** and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent/**assent** form is to be signed and personally dated by the subject and by the person who conducted the informed consent/**assent** discussion. The original signed informed consent/**assent** form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent/**assent** form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent/**assent** form to attest that informed consent/**assent** was freely given and understood.

Section: 11.2 Institutional Review Board/Independent Ethics Committee

Add:

A copy of the protocol, proposed informed consent/**assent** form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent/**assent** form must be received by Amgen before study can be executed.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent/**assent** document.

Section: 11.3 Subject Confidentiality

Add:

- Documents that are not for submission to Amgen (eg, signed informed consent/**assent** forms, as applicable) are to be kept in confidence by the investigator, except as described below.

Section: 13 Appendix A

Replace:

The Common Terminology Criteria for Adverse Events (CTCAE) version ~~3~~.0 will be used for adverse event grading. The CTCAE version ~~3~~.0 is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

With:

The Common Terminology Criteria for Adverse Events (CTCAE) version **4**.0 will be used for adverse event grading. The CTCAE version **4**.0 is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Section: 13 Appendix B

Replace:

Sample serious adverse event report form replaced with current version.